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SYNTHESIS AND KINETICS OF THE CYCLIZATION OF 3-(DIALKYLAMINOPHENYL)-2-(PHENYLCARBONYL)-PROP-2-ENENITRILES

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The reaction of ortho-(N,N-dialkylamino)benzaldehydes with benzoylacetonitrile gave fused 1,2,3,4-tetrahydroquinolino-5-carbonitriles due to cyclization of the intermediate 2-(phenylcarbonyl)-3-[2-[(dialkylamino)phenyl]prop-2-enenitriles through a tert-amino effect mechanism. Kinetic studies were carried out on the cyclization of 2-(phenylcarbonyl)-3-[2-(piperidin-1-yl)phenyl]prop-2-enenitrile.

Keywords: *N*,*N*-dialkyl-*o*-vinylanilines, 1,2,3,4-tetrahydroquinolines, *tert*-amino effect, cyclization, reaction kinetics, stereoselectivity.

The considerable interest in tetrahydroquinolines and their derivatives is primarily due to the biological activity of tetrahydroquinolines themselves [1, 2], as well as their remarkable reactivity and the variety of chemical transformations, which make these compounds convenient building blocks in the synthesis of other structures with high biological activity [3]. One method for the synthesis of tetrahydroquinoline systems is the cyclization of *N,N*-dialkyl-*o*-vinylanilines proceeding through a *tert*-amino effect mechanism [4-7].

We studied the reaction of 2-dialkylaminobenzaldehydes **1a-i** with benzoylacetonitrile (**2**), leading to *N*,*N*-dialkyl-*o*-vinylanilines **3a-i**, which, in turn, cyclized to the condensed 1,2,3,4-tetrahydroquinolino-5-carbonitriles **4a-i**. Examination of the literature showed that an analogous reaction has been carried out only using *o*-piperidinobenzaldehyde as the starting reagent [8].

Knoevenagel condensation products **3a-e**,**h**,**i** could not be isolated in the condensation of 2-piperidinobenzaldehydes **1a-e**,**h**,**i**, since the cyclization to give 1,2,3,4-tetrahydroquinolino-5-carbonitriles **4a-e**,**h**,**i** dominated under these reaction conditions [9]. Knoevenagel condensation products **3f**,**g**, that did not undergo cyclization in toluene, were isolated only in the case of benzaldehydes **1f**,**g**. This finding may be attributed to the lower basicity of the morpholine and piperazine dialkylamino groups. 1,2,3,4-Tetrahydroquinolino-5-carbonitriles **4f**,**g** were obtained by the cyclization of *N*,*N*-dialkyl-*o*-vinylanilines **3f**,**g** upon heating in 1-butanol at reflux.

1,2,3,4-Tetrahydroquinolino-5-carbonitriles **4a-i** contain from two to four asymmetric sites.

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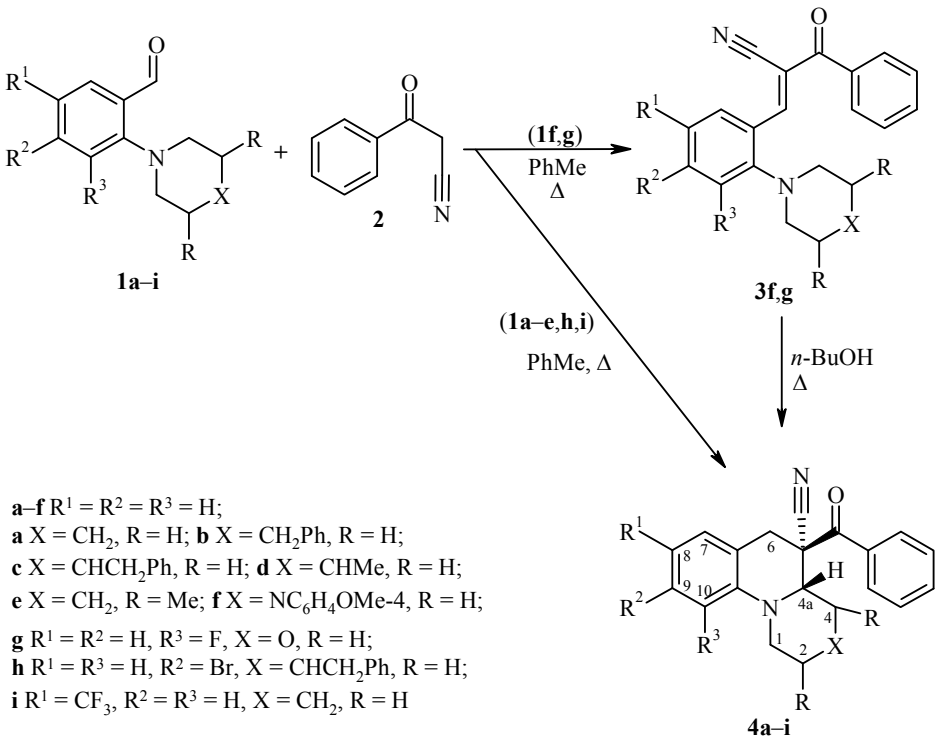
We have already established that the cyclization of dialkyl-*ortho*-vinylanilines containing substituents in the β- and γ-positions relative to the nitrogen atom of the cyclic amino group proceeded with high stereo- and regioselectivity [9, 10] when using cyclic CH active compounds such as barbituric acids, Meldrum's acid, cyclohexanediones, and asymmetric 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one. In this case, the formation of the spiro-coupled 2,3,4,4a,5,6-hexahydro-6*H*-benzo[*c*]quinolizines with axial orientation of the hydrogen atoms at positions 3 (or 2 and 4 in the case of β-substitution) and 4a was observed.



a–**f** $R^1 = R^2 = R^3 = H$;
a X = CH_2, R = H; **b** X = CH_2Ph, R = H;
c X = $CHCH_2Ph$, R = H; **d** X = CHMe, R = H;
e X = CH_2, R = Me; **f** X = NC_6H_4OMe-4, R = H;
g $R^1 = R^2 = H$, $R^3 = F$, X = O, R = H;
h $R^1 = R^3 = H$, $R^2 = Br$, X = $CHCH_2Ph$, R = H;
i $R^1 = CF_3$, $R^2 = R^3 = H$, X = CH_2, R = H

On the other hand, the reaction with malononitrile produced a 1:1 mixture of two diastereomers [10].

The ^1H and ^{13}C NMR spectral data indicated the formation of predominantly one diastereomer also by cyclization of vinyl derivatives **3a-i** using benzoylacetonitrile. The diastereoselective excess of the isolated products after crystallization from ethanol was not less than 80%.

The complete assignment of all the aliphatic and aromatic proton signals was accomplished by analysis of the 2D ^1H–^{13}C HSQC and ^1H–^{13}C HMBC experiments.

The H-4a proton in all the cyclization products was found in the axial position. The hydrogen atom at position 3 in compounds **4b**-**d**,**h** and the protons at positions 2 and 4 in compound **4e** were also axial. On the basis of our previous results [11], we proposed that the nitrile group in the major reaction product was oriented axially, while the benzoyl group was equatorial; the reverse arrangement of these substituents was correspondingly found for the minor product. This hypothesis was confirmed by X-ray structural analysis for nitrile **4e** (Fig. 1). The H-2, H-4, and H-4a atoms were all axial. The equatorial benzoyl group was found in the *cis* position, while the axial nitrile group was in the *trans* position relative to these hydrogen atoms. The two methyl substituents of the piperidine fragment were oriented equatorially.

The formation of two diastereomers through cyclization of *N*,*N*-dialkyl-*o*-vinylanilines may be attributed to two possible reasons: either the formation of the two products occurred due to irreversible competing reactions or the cyclization was reversible, i.e., the thermodynamically more stable isomer was formed. In order to clarify this question, kinetic studies were carried out on the cyclization of 3-[2-(piperidin-1-yl)phenyl]-2-(phenylcarbonyl)prop-2-enenitrile (**3a**) using ^1H NMR spectroscopy.

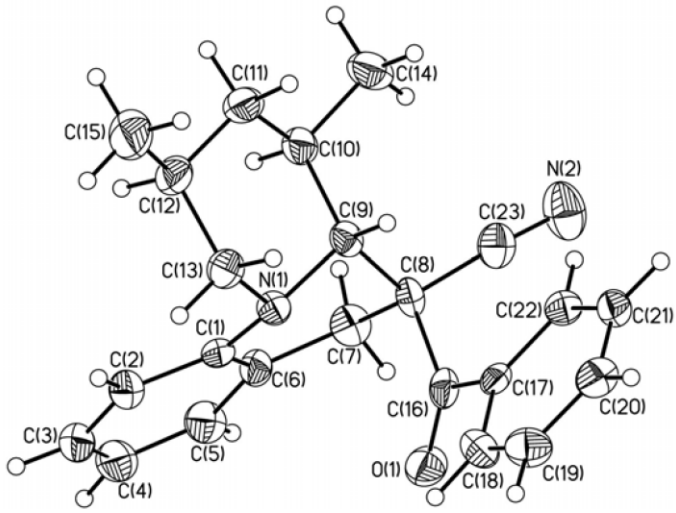
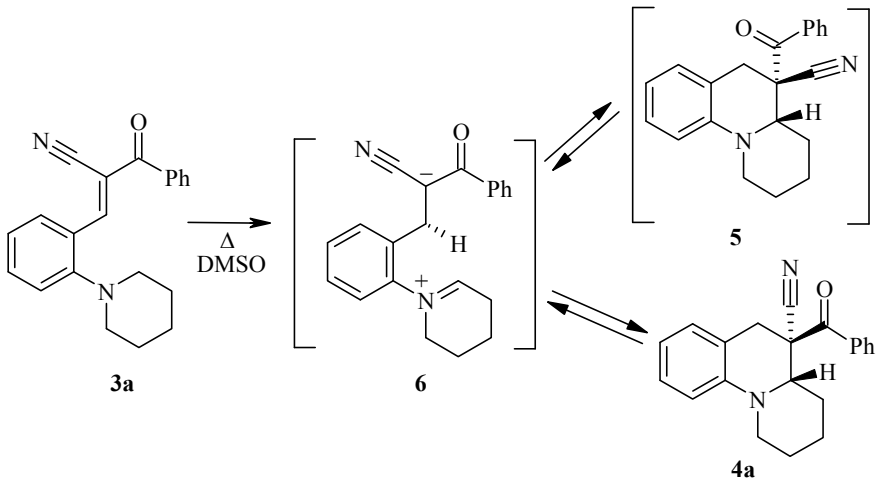


Fig. 1. Molecular structure of nitrile **4e** with representation of the hydrogen atoms by thermal vibration ellipsoids of 50% probability.

Figure 2 presents spectra characterizing the cyclization over time at 90°C in DMSO. The rate was monitored relative to the diminishing integral intensity of the vinyl group hydrogen singlet in the vicinity of 8 ppm. The accumulation of the cyclization products was monitored from the growth of the signals for tertiary amino group α-CH protons in the vicinity of 4 ppm. These signals were broadened doublets with the following chemical shifts, δ, ppm: 4.22 for product **5** and 4.01 for product **4a** (1-CH*eq*), and 4.16 for product **5** and 3.73 for product **4a** (4a-CH*ax*).



The reaction followed a first-order kinetic equation relative to starting nitrile **3a**. The rate constants were found as the mean values from three parallel experiments. The relative error at the 0.99 confidence level for determination of the rate constants and activation parameters did not exceed 5%. The observed rate constants and reaction half-lives are given in Table 1.

Figure 3 gives the dependence of the molar concentrations of the starting reagent **3a** (curve *1*), major product **4a** (curve *3*), and minor product **5** (curve *2*) on elapsed time. The kinetic curves for the cyclization of 3-[2-(piperidin-1-yl)phenyl]-2-(phenylcarbonyl)prop-2-enenitrile (**3a**) clearly show that the ratio of the products varied over time (Fig. 4). Thus, the conversion of nitrile **3a** did not occur through irreversible parallel cyclization reactions, but rather by a reversible process. This hypothesis is in complete accord with the literature data [2].

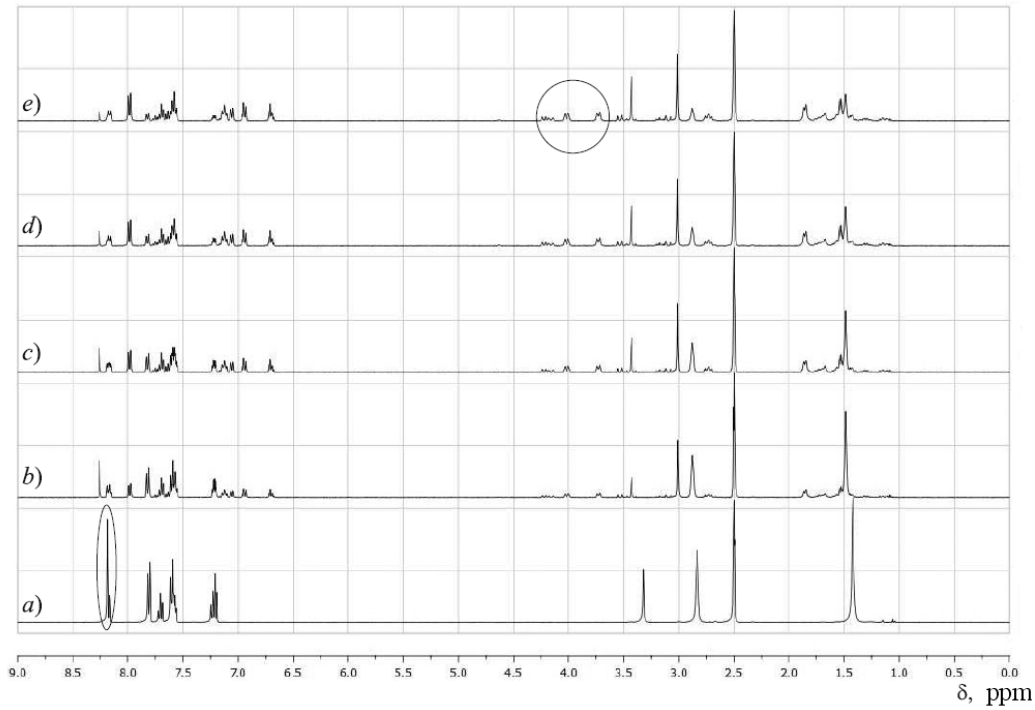


Fig. 2. ^{1}H NMR spectra characterizing the course of the nitrile **3a** cyclization over time: *a* – spectrum of the starting compound, *b* – spectrum of the reaction mixture after 18 min, *c* – after 34 min, *d* – after 50 min, and *e* – after 66 min.

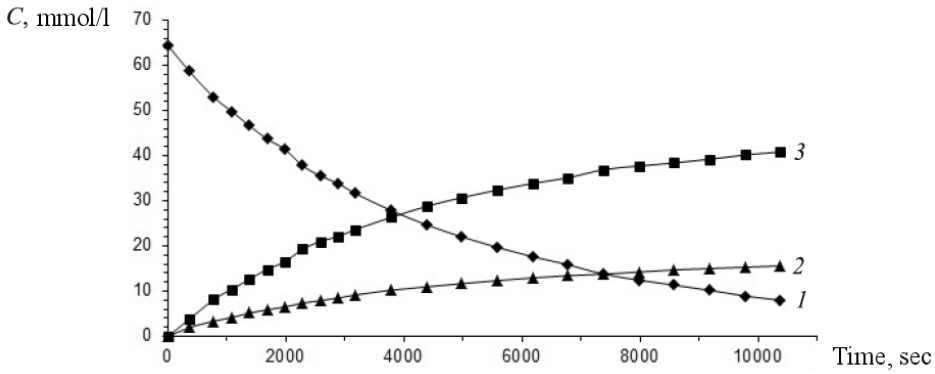


Fig. 3. Kinetic curves for the cyclization of starting nitrile **3a** (*1*) and reaction products **5** (*2*) and **4a** (*3*) at 80°C.

On the basis of our kinetic results and literature data [2], we propose that two products were formed, namely, a kinetic control product **5** and a thermodynamic control product **4a**. The interconversion of these two isomers occurred under the reaction conditions through dipolar intermediate **6**, obtained as a result of a [1,5] hydride shift. This reaction predominantly yielded the thermodynamically preferred stereoisomer **4a**.

A study of the cyclization at various temperatures permitted us to use the Eyring equation [12] to calculate the major activation parameters for this reaction: activation free energy $\Delta G^{\neq}$ = 107±5 kJ/mol (at 298 K (25°C)) and 112.9±5.8 kJ/mol (at 363 K (90°C)), activation enthalpy $\Delta H^{\neq}$ = 80.1±2.5 kJ/mol, activation entropy $\Delta S^{\neq}$ = -90.2±7 J/(mol·K), and reaction activation energy E_a = 83.1±2.5 kJ/mol. These values were quite comparable to the data of Groenen et al. [13] obtained in a study of [2-(pyrrolidinyl)(phenyl)methylidene]-

TABLE 1. Reaction Rate Constants (k) and Half-Lives ($\tau_{½}$) of Starting Nitrile **3a**, Depending on the Reaction Temperature

T,°C	k, 10^{-4} sec^{-1}	$\tau_{½}$, min	Determination coefficient, R^2
70	0.84±0.04	137	0.998
80	2.02±0.11	57	0.995
90	4.60±0.25	25	0.998
98	7.27±0.39	16	0.999
100	9.20±0.51	13	0.998

propanedinitrile cyclization to 1,2,3,3a,4,5-hexahydropyrrolo[1,2-*a*]-quinoline-4,4-dicarbonitrile at 90°C: $\Delta G^{\neq}$ = 26.6±0.8 kcal/mol (111.7±3.4 kJ/mol), $\Delta H^{\neq}$ = 22.2±0.4 kcal/mol (93.24±1.68 kJ/mol), $\Delta S^{\neq}$ = -12.0±1.1 kcal/(mol·K) (-50.4±4.62 J/(mol·K)). The rate constants found in a study of 1,3-dimethyl-5-(2-dimethylamino-4-nitrobenzylidene)barbituric acid cyclization to 1,1',3-trimethyl-6'-nitro-1',4'-dihydro-2*H*,2'*H*-spiro[pyrimidine-5,3'-quinoline]-2,4,6(1*H*,3*H*)-trione were as follows: $k = 2.3 \cdot 10^{-5}$ sec^{-1} at 60°C, $1.6 \cdot 10^{-4}$ sec^{-1} at 80°C, and $1.2 \cdot 10^{-3}$ sec^{-1} at 100°C, E_a = 24.5±0.5 kcal/mol or 102.9±2/1 kJ/mol. These values were greater than those found for our reaction, although the cyclization to give spirocyclic analogs proceeded more readily [14].

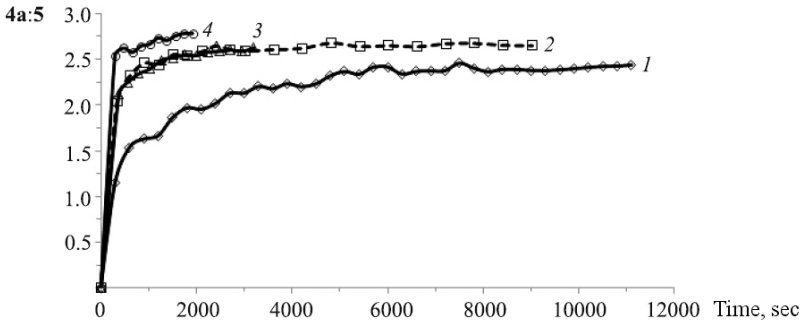


Fig. 4. Cyclization product ratio (**4a:5**) during the reaction at different temperatures: *1* – 70°C, *2* – 80°C, *3* – 90°C, and *4* – 100°C.

The negative value of the activation entropy obtained in our study reflected a highly organized transition state. The low value of the calculated activation energy may reflect pericyclic nature for the [1,5] hydride shift, which was the rate-limiting step for the cyclization.

Thus, fused derivatives of 1,2,3,4-tetrahydroquinoline may be obtained in a reaction of *ortho*-dialkylaminobenzaldehydes with benzoylacetonitrile without isolation of intermediate *N*,*N*-dialkyl-*o*-vinylanilines. The kinetics of 3-[2-(piperidin-1-yl)phenyl]-2-(phenylcarbonyl)prop-2-enenitrile cyclization were under thermodynamic control.

EXPERIMENTAL

The IR spectra were recorded on a Bruker Alpha spectrophotometer. The ^{1}H, ^{19}F, and ^{13}C NMR spectra were acquired on a Bruker Avance II spectrometer at 400, 376, and 100 MHz, respectively with TMS as internal standard, at the Laboratory of Complex Investigation and Expert Evaluation of Organic Materials of

The Collective Use Center of Ural Federal University. The electron impact mass spectra were acquired on a MAT II mass spectrometer at 70 eV. The melting points were measured on a Stuart SMP3 instrument and were not corrected. The elemental analysis was carried out on a PE 2400 Series II CHNS analyzer. Halogen content was determined by Schöniger combustion [15]. The reaction progress and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with 1:1 and 1:2 ethyl acetate–hexane as the eluent and visualization by UV light or iodine vapor.

***o*-Dialkylaminobenzaldehydes 1a-i** were obtained in 60-80% yield by nucleophilic substitution of the fluorine atom in 2-fluorobenzaldehydes with the corresponding cyclic dialkylamines according to our previous procedure [9]. A commercial sample of 2-fluorobenzaldehyde was obtained from Acros.

3-[2-(Piperidin-1-yl)phenyl]-2-(phenylcarbonyl)prop-2-enenitrile (3a). Benzoylacetonitrile (**2**) (0.29 g, 2.0 mmol) and proline (0.023 g, 0.2 mmol) were added to a solution of benzaldehyde **1a** (0.38 g, 2.0 mmol) in ethanol (10 ml), and the reaction mixture was left at room temperature for several days. The solvent was evaporated under vacuum, and the solid residue was recrystallized from ethanol. Yield 0.42 g (66%). Orange crystals. Mp 125-126°C. IR spectrum, ν, cm^{-1}: 1650 (C=O), 2210 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.25 (1H, s, CH); 8.19 (1H, dd, *J* = 7.6, *J* = 1.2, H Ar); 7.81-7.78 (2H, m, H Ph); 7.68 (1H, tt, *J* = 7.6, *J* = 1.6, H-4 Ph); 7.56 (2H, dd, *J* = 7.6, *J* = 7.2, H Ph); 7.53 (1H, ddd, *J* = 8.4, *J* = 7.6, *J* = 1.2, H Ar); 7.18 (1H, t, *J* = 7.6, H Ar); 7.16 (1H, d, *J* = 7.6, H Ar); 2.90-2.84 (4H, m, CH_2NCH_2); 1.54-1.47 (6H, m, $3CH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 317 $[M+H]^+$ (18), 316 $[M]^+$ (83), 211 (81), 172 (63), 105 (100), 91 (7), 77 (71). Found, %: C 79.74; H 6.36; N 8.81. $C_{21}H_{20}N_2O$. Calculated, %: C 79.72; H 6.37; N 8.85.

***N*,*N*-Dialkyl-*o*-vinylanilines 3f,g and 2,3,4,4a,5,6-hexahydroquinolines 4a-e,h,i (General Method)**. Benzoylacetonitrile (**2**) (1.0 mmol) was added to a solution of the corresponding benzaldehyde **1a-i** (1.0 mmol) in toluene (10 ml) and heated at reflux on a glycerin bath for 5-10 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuum. The residue was recrystallized from ethanol.

3-{2-[4-(4-Methoxyphenyl)piperazin-1-yl]phenyl}-2-(phenylcarbonyl)prop-2-enenitrile (3f). Yield 0.15 g (88%). Orange crystals. Mp 158-159°C. IR spectrum, ν, cm^{-1}: 1660 (C=O), 2200 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.31 (1H, s, CH); 8.22 (1H, d, *J* = 8.0, H Ar); 7.81 (2H, d, *J* = 7.2, H-2,6 Ph); 7.61 (1H, ddt, *J* = 7.6, *J* = 7.2, *J* = 2.4, H-4 Ph); 7.59-7.52 (3H, m, H Ar); 7.24 (2H, t, *J* = 8.0, H-3,5 Ph); 6.84-6.76 (4H, m, C_6H_4OMe); 3.72 (3H, s, OCH_3); 3.08-3.04 (4H, m, $2CH_2$); 2.99-2.97 (4H, m, $2CH_2$). Mass spectrum, *m*/*z* (I_{rel}, %): 424 $[M+H]^+$ (30), 423 $[M]^+$ (100), 316 (10), 164 (29), 150 (31), 105 (35), 77 (26). Found, %: C 76.53; H 5.94; N 9.89. $C_{27}H_{25}N_3O_2$. Calculated, %: C 76.57; H 5.95; N 9.92.

3-[3-Fluoro-2-(morpholin-4-yl)phenyl]-2-(phenylcarbonyl)prop-2-enenitrile (3g). Yield 0.14 g (67%). Bright-yellow crystals. Mp 113-114°C. IR spectrum, ν, cm^{-1}: 1660 (C=O), 2220 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.42 (1H, s, CH); 8.04 (1H, dd, *J* = 7.6, *J* = 1.2, H Ar); 7.86-7.84 (2H, m, H-2,6 Ph); 7.74 (1H, tt, *J* = 7.6, *J* = 1.2, H-4 Ph); 7.62 (2H, dd, *J* = 8.0, *J* = 7.2, H-3,5 Ph); 7.52 (1H, ddd, *J* = 12.8, *J* = 8.4, *J* = 1.6, H Ar); 7.43 (1H, ddd, *J* = 11.2, *J* = 8.0, *J* = 5.2, H Ar); 3.45-3.38 (4H, m, CH_2OCH_2); 3.03-2.96 (4H, m, CH_2NCH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 190.6 (C=O); 159.4 (d, *J* = 249.6, C–F); 152.05 (d, *J* = 3.3, C=C); 139.2 (d, *J* = 10.9, C Ar); 135.8 (C Ph); 132.9 (C Ph); 130.8 (d, *J* = 5.5, C Ar); 129.0 (C Ph); 128.6 (C Ph); 126.3 (d, *J* = 8.7, C Ar); 124.7 (d, *J* = 2.9, C Ar); 121.2 (d, *J* = 20.7, C Ar); 115.8 (CN); 112.3 (C=C); 66.7 (2C–O); 51.8 (d, *J* = 4.5, 2C–N). Mass spectrum, *m*/*z* (I_{rel}, %): 337 $[M+H]^+$ (4), 336 $[M]^+$ (21), 105 (100), 77 (49). Found, %: C 71.41; H 5.06; F 5.64; N 8.35. $C_{20}H_{17}FN_2O_2$. Calculated, %: C 71.42; H 5.09; F 5.65; N 8.33.

5-(Phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4a). Yield 0.17 g (33%). Beige crystals. 113-114°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 2230 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.02 (2H, d, *J* = 7.2, H-2,6 Ph); 7.67 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.55 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.09 (1H, td, *J* = 7.2, *J* = 1.2, H Ar); 7.02 (1H, d, *J* = 7.2, H Ar); 6.88 (1H, d, *J* = 8.0, H Ar); 6.68 (1H, t, *J* = 7.2, H Ar); 4.01 (1H, br. d, *J* = 13.2, 1-CH*eq*); 3.73 (1H, dd, *J* = 9.2, *J* = 1.6, 4a-CH*ax*); 3.40 (2H, AB system, *J* = 16.0, 6-CH_2); 2.68 (1H, ddd, *J* = 14.8, *J* = 12.4, *J* = 3.2, 1-CH*eq*); 1.88 (2H, br. d, *J* = 7.6, 2,4-CH*eq*); 1.69–1.44 (4H, m, 2,4-CH*ax*, 3-CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm:

193.5 (C=O); 143.7; 135.3; 133.3; 129.1; 128.8; 128.5; 128.2; 119.3; 118.7; 118.4 (CN); 113.7; 60.8 (C–N); 50.0; 48.7 (C–N); 35.6; 27.3; 24.2; 23.5. Mass spectrum, *m/z* (I_{rel}, %): 317 $[M+H]^+$ (15), 316 $[M]^+$ (60), 211 (78), 172 (60), 105 (100), 91 (8), 77 (91). Found, %: C 79.76; H 6.34; N 8.82. $C_{21}H_{20}N_2O$. Calculated, %: C 79.72; H 6.37; N 8.85.

3-Phenyl-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4b). Yield 0.12 g (34%). Light-brown crystals. Mp 109-110°C (decomp.). IR spectrum, ν, cm^{-1}: 1680 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.23 (2H, dd, *J* = 7.6, *J* = 1.2, H-2,6 Ph); 7.73 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.61 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.17-7.05 (5H, m, H Ph); 6.99 (3H, d, *J* = 7.6, H Ar); 6.72 (1H, dd, *J* = 7.6, *J* = 7.2, H Ar); 4.42 (1H, br. d, *J* = 11.2, 1-CH*eq*); 4.31 (1H, br. d, *J* = 14.6, 4a-CH*ax*); 3.62 (1H, d, *J* = 16.8, 6-CH*eq*); 3.36 (1H, ddd, *J* = 12.4, *J* = 12.0, *J* = 2.4, 1-CH*ax*); 3.06 (1H, d, *J* = 16.8, 6-CH*ax*); 2.87 (1H, tt, *J* = 12.0, *J* = 3.8, 3-CH*ax*); 1.66 (1H, br. dd, *J* = 12.8, *J* = 2.6, 2-CH*eq*); 1.60 (1H, ddd, *J* = 16.0, *J* = 12.8, *J* = 3.8, 4-CH*eq*); 1.43 (1H, td, *J* = 12.2, *J* = 12.0, 4-CH*ax*); 1.24 (1H, br. dd, *J* = 10.4, *J* = 2.6, 2-CH*ax*). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 191.0 (C=O); 144.3; 142.3; 134.2; 134.1; 130.2; 129.4; 129.0; 128.5 (2C); 126.6; 120.0; 118.4 (CN); 118.3; 113.2; 61.0 (C–N); 49.0; 47.9 (C–N); 43.5; 31.4; 31.3; 29.6. Mass spectrum, *m/z* (I_{rel}, %): 393 $[M+H]^+$ (17), 392 $[M]^+$ (53), 287 (41), 248 (25), 183 (18), 105 (100), 91 (19), 77 (75). Found, %: C 82.59; H 6.15; N 7.12. $C_{27}H_{24}N_2O$. Calculated, %: C 82.62; H 6.16; N 7.14.

3-Benzyl-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4c). Yield 0.27 g (53%). White needles. Mp 131-132°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.95 (2H, d, *J* = 7.2, H-2,6 Ph); 7.66 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.54 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.24 (2H, dd, *J* = 7.6, *J* = 6.8, H Ph); 7.17-7.10 (3H, m, H Ph); 7.08 (1H, dd, *J* = 8.8, *J* = 8.4, H Ar); 7.03 (1H, d, *J* = 6.8, H Ar); 6.86 (1H, d, *J* = 8.0, H Ar); 6.69 (1H, dd, *J* = 7.2, H Ar); 3.99 (1H, br. d, *J* = 13.2, 1-CH*eq*); 3.70 (1H, dd, *J* = 11.6, *J* = 2.0, 4a-CH*ax*); 3.39 (2H, dd, *J* = 16.0, *J* = 16.0, 6-CH_2); 2.62 (1H, ddd, *J* = 13.2, *J* = 10.8, *J* = 2.4, 1-CH*ax*); 2.57 (1H, d, *J* = 6.8) and 2.45 (1H, dd, *J* = 7.2, *J* = 5.2, CH_2Ph); 1.87 (2H, br. d, *J* = 10.4, 2,4-CH*eq*); 1.60 (1H, br. d, *J* = 13.2, 2-CH*ax*); 1.28-1.19 (2H, m, 3,4-CH*ax*). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 193.7 (C=O); 143.6; 139.5; 135.3; 133.3; 129.2; 129.0; 128.7; 128.5; 128.3; 128.2; 126.1; 119.2; 118.7; 118.5 (CN); 113.7; 60.3 (C–N); 50.0; 48.1 (C–N); 43.0 (CH_2); 38.1 (CH_2); 35.8; 34.0; 29.7. Mass spectrum, *m/z* (I_{rel}, %): 407 $[M+H]^+$ (20), 406 $[M]^+$ (65), 315 (25), 301 (46), 105 (100), 91 (37), 77 (67). Found, %: C 82.72; H 6.41; N 6.91. $C_{28}H_{26}N_2O$. Calculated, %: C 82.73; H 6.45; N 6.89.

3-Methyl-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4d). Yield 0.26 g (58%). Beige crystals. Mp 115-117°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 2250 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.22 (2H, dd, *J* = 7.2, *J* = 1.2, H-2,6 Ph); 7.73 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.61 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.11 (1H, t, *J* = 7.6, H Ar); 7.08 (1H, d, *J* = 6.4, H Ar); 6.91 (1H, d, *J* = 8.4, H Ar); 6.68 (1H, dd, *J* = 7.2, *J* = 6.8, H Ar); 4.22 (1H, br. d, *J* = 11.6, 1-CH*eq*); 4.18 (1H, br. d, *J* = 16.8, 4a-CH*ax*); 3.54 (1H, d, *J* = 16.8, 6-CH*eq*); 3.16 (1H, ddd, *J* = 12.8, *J* = 11.2, *J* = 2.0, 1-CH*ax*); 3.01 (1H, d, *J* = 16.8, 6-CH*ax*); 1.72-1.58 (1H, m, 2-CH*eq*); 1.47 (1H, dd, *J* = 13.6, *J* = 2.0, 4-CH*eq*); 1.11-1.06 (1H, m, 2-CH*ax*); 1.05 (1H, br. d, *J* = 12.6, 3-CH*ax*); 0.89 (1H, ddd, *J* = 12.0, *J* = 12.4, *J* = 11.6, 4-CH*ax*); 0.78 (3H, d, *J* = 6.4, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 193.5 (C=O); 143.6; 135.2; 134.2; 133.4; 130.2; 129.0; 128.8; 128.4; 118.7; 118.4 (CN); 113.7; 60.2 (C–N); 49.9; 48.3 (C–N); 35.7; 32.4; 32.0; 31.2; 21.8 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 331 $[M+H]^+$ (18), 330 $[M]^+$ (72), 225 (73), 186 (51), 105 (100), 77 (81). Found, %: C 79.95; H 6.75; N 8.45. $C_{22}H_{22}N_2O$. Calculated, %: C 79.97; H 6.71; N 8.48.

2,4-Dimethyl-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4e). Yield 0.3 g (48%). Pale-yellow crystals. Mp 130-131°C. IR spectrum, ν, cm^{-1}: 1700 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.99 (2H, dd, *J* = 7.2, *J* = 1.2, H-2,6 Ph); 7.66 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.56 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.13 (1H, d, *J* = 7.2, H Ar); 7.07 (1H, ddd, *J* = 8.4, *J* = 7.2, *J* = 1.2, H Ar); 6.72 (1H, d, *J* = 8.0, H Ar); 6.68 (1H, dd, *J* = 7.6, *J* = 7.2, H Ar); 3.76 (1H, br. d, *J* = 10.0, 1-CH*eq*); 3.74 (1H, br. d, *J* = 14.0, 4a-CH*ax*); 3.22 (2H, dd, *J* = 15.2, *J* = 15.2, 6-CH_2); 2.25 (1H, dd,

J = 14.0, *J* = 11.6, 1-CH*ax*); 1.78-1.66 (3H, m, 2CH*ax*, CH*eq*); 1.06 (1H, q, *J* = 12.8, *J* = 11.6, *J* = 9.6, CH*ax*); 1.01 (3H, d, *J* = 6.4, CH_3); 0.82 (3H, d, *J* = 6.4, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 191.1 (C=O); 143.4; 134.8; 132.9; 128.8; 128.5; 128.4; 128.2; 120.5; 119.3; 118.2 (CN); 113.3; 65.8 (C–N); 55.8 (C–N); 44.1; 34.1; 33.0; 27.6; 19.2 (CH_3); 18.5 (CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 345 $[M+H]^+$ (16), 344 $[M]^+$ (61), 200 (29), 155 (16), 105 (100), 77 (69). Found, %: C 80.23; H 7.02; N 8.15. $C_{23}H_{24}N_2O$. Calculated, %: C 80.20; H 7.02; N 8.13.

3-Benzyl-9-bromo-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4f). Yield 0.164 g ((48%). Beige crystals. Mp 136-137°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.93 (2H, d, *J* = 7.6, H-2,6 Ph); 7.71 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.58 (2H, dd, *J* = 7.6, H-3,5 Ph); 7.30-7.08 (6H, m, H Ar); 7.02 (1H, d, *J* = 8.0, H Ar); 6.86 (1H, d, *J* = 8.2, H Ar); 4.00 (1H, br. d, *J* = 12.2, 1-CH*eq*); 3.74 (1H, br. d, *J* = 10.2, 4a-CH*ax*); 3.43 (2H, AB system, *J* = 16.0, 6-CH_2); 2.72-2.60 (3H, m, 1-CH*ax*, CH_2); 1.82 (2H, m, 2,4-CH*eq*); 1.58 (1H, br. d, *J* = 12.8, 2-CH*ax*); 1.26-1.17 (2H, m, 3,4-CH*ax*). Mass spectrum, *m*/*z* (I_{rel}, %): 487 (10), 486 [M (^{81}Br)]$^+$ (31), 485 (16), 484 [M (^{79}Br)]$^+$ (30), 381 (19), 379 (21), 105 (100), 91 (24), 77 (41). Found, %: C 69.27; H 5.22; Br 16.41; N 5.75. $C_{28}H_{25}BrN_2O$. Calculated, %: C 69.28; H 5.19; Br 16.46; N 5.77.

5-(Phenylcarbonyl)-8-(trifluoromethyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (4i). Yield 0.14 g (39%). White crystals. Mp 119-120°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.04 (2H, d, *J* = 7.2, H-2,6 Ph); 7.69 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.56 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.36-7.35 (2H, m, H Ar); 7.02 (1H, d, *J* = 9.6, H Ar); 4.09 (1H, br. d, *J* = 13.6, 1-CH*eq*); 3.88 (1H, dd, *J* = 10.8, *J* = 1.6, 4a-CH*ax*); 3.52 (1H, d, *J* = 16.0, 6-CH*eq*); 3.41 (1H, *J* = 16.4, 6-CH*ax*); 2.80 (1H, ddd, *J* = 12.4, *J* = 10.4, *J* = 2.0, 1-CH*ax*); 1.88-1.94 (2H, m, 2,4-CH*eq*); 1.71-1.49 (4H, m, 3-CH_2, 2,4-CH*ax*). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: -60.6 (3F, s, CF_3). Mass spectrum, *m*/*z* (I_{rel}, %): 385 $[M+H]^+$ (12), 384 $[M]^+$ (46), 279 (54), 240 (33), 105 (100), 77 (58). Found, %: C 68.71; H 4.95; F 14.81; N 7.23. $C_{22}H_{19}F_3N_2O$. Calculated, %: C 68.74; H 4.98; F 14.83; N 7.29.

Preparation of Hexahydroquinolines 4f,g (General Method). Corresponding *N*,*N*-dialkyl-*o*-vinylaniline **3f**,**g** (1.0 mmol) in 1-butanol (15 ml) was heated at reflux for 5-10 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuum. The residue was crystallized from ethanol.

3-(4-Methoxyphenyl)-5-(phenylcarbonyl)-2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinolino-5-carbonitrile (4f). Yield 0.06 g (62%). Beige crystals. Mp 88-90°C (decomp.). IR spectrum, ν, cm^{-1}: 1680 (C=O), 2240 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.13 (2H, dd, *J* = 7.2, *J* = 1.2, H-2,6 Ph); 7.71 (1H, dd, *J* = 7.6, *J* = 7.2, H-4 Ph); 7.59 (2H, dd, *J* = 8.0, *J* = 7.6, H-3,5 Ph); 7.16 (1H, ddd, *J* = 8.4, *J* = 7.2, *J* = 1.2, H Ar); 7.06 (1H, d, *J* = 6.4, H Ar); 7.02 (1H, d, *J* = 8.2, H Ar); 6.89-6.85 (2H, m, H Ar); 6.79-6.74 (3H, m, H Ar); 4.08 (1H, br. d, *J* = 11.6, 1-CH*eq*); 3.88 (1H, dd, *J* = 10.0, *J* = 2.8, 4a-CH*ax*); 3.71 (3H, s, OCH_3); 3.63 (1H, d, *J* = 16.0, 6-CH*eq*); 3.58-3.55 (2H, m, 2,4-CH*eq*); 3.42 (1H, d, *J* = 16.4, 6-CH*ax*); 3.05 (1H, ddd, *J* = 12.0, *J* = 8.8, *J* = 3.2, 1-CH*ax*); 2.90 (1H, ddd, *J* = 14.0, *J* = 11.2, *J* = 2.0, 2-CH*ax*); 2.74 (1H, ddd, *J* = 11.2, *J* = 10.8, *J* = 2.8, 4-CH*ax*). Mass spectrum, *m*/*z* (I_{rel}, %): 424 $[M+H]^+$ (29), 423 $[M]^+$ (100), 316 (18), 164 (35), 105 (37), 77 (28). Found, %: C 76.56; H 5.97; N 9.91. $C_{27}H_{25}N_3O_2$. Calculated, %: C 76.57; H 5.95; N 9.92.

10-Fluoro-5-(phenylcarbonyl)-1,2,4,4a,5,6-hexahydro[1,4]oxazino[4,3-*a*]quinolino-5-carbonitrile (4g). Yield 0.20 g (89%). Beige crystals. Mp 151-152°C. IR spectrum, ν, cm^{-1}: 1680 (C=O), 2200 (C=N). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.11-8.08 (2H, m, H-2,6 Ph); 7.75 (1H, ddt, *J* = 7.6, *J* = 7.2, *J* = 1.2, H-4 Ph); 7.64-7.59 (2H, m, H-3,5 Ph); 7.09 (1H, ddd, *J* = 14.4, *J* = 8.0, *J* = 0.8, H Ar); 7.01 (1H, d, *J* = 7.2, H Ar); 6.87 (1H, ddd, *J* = 10.8, *J* = 8.0, *J* = 4.8, H Ar); 4.04 (1H, ddd, *J* = 12.8, *J* = 6.4, *J* = 3.2, 1-CH*eq*); 3.92 (1H, dd, *J* = 10.8, *J* = 2.8, 4-CH*eq*); 3.87 (1H, ddd, *J* = 11.6, *J* = 3.2, *J* = 3.2, 2-CH*eq*); 3.79 (1H, dd, *J* = 8.8, *J* = 2.8, 4a-CH*ax*); 3.76 (1H, ddd, *J* = 11.6, *J* = 8.8, *J* = 2.8, 2-CH*ax*); 3.69 (1H, d, *J* = 16.0, 6-CH*eq*); 3.55 (1H, dd, *J* = 11.2, *J* = 10.8, 4-CH*ax*); 3.50 (1H, d, *J* = 16.0, 6-CH*ax*); 3.22 (1H, ddd, *J* = 12.8, *J* = 9.6, *J* = 3.2, 1-CH*ax*). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 194.0 (C=O); 152.6 (d, *J* = 242.9, C–F); 134.8 (C Ph); 134.1 (C Ph); 132.5 (d, *J* = 6.9, C Ar); 128.9 (C Ph); 128.8 (C Ph); 125.5 (d, *J* = 2.5, C Ar); 123.8 (d, *J* = 3.0, C Ar); 120.4 (d, *J* = 8.7, C Ar); 118.8 (CN); 115.8 (d, *J* = 22.0, C Ar); 67.3 (C–O); 66.4 (C–O); 59.9 (C–N); 49.6 (d, *J* = 13.8,

C–N); 46.3; 37.8 (CH_2). ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: -121.7 (1F, s, CF Ar). Mass spectrum, *m/z* (I_{rel}, %): 337 $[M+H]^+$ (17), 336 $[M]^+$ (42), 105 (100), 77 (54). Found, %: C 71.38; H 5.07; F 5.68; N 8.34. $C_{20}H_{17}FN_2O_2$. Calculated, %: C 71.42; H 5.09; F 5.65; N 8.33.

X-ray structural study of quinolinocarbonitrile 4e was carried out on an Xcalibur-3 diffractometer (Oxford Diffraction) with a CCD detector (λ(MoKα) 0.71073 Å, graphite monochromator, ω-scanning, scanning step 1°, 295(2) K). The unit cell parameters of colorless orthorhombic crystals of 2,4-dimethyl-5-(phenylcarbonitrile)-2,3,4,4a,5,6-hexahydro-1*H*-pyrido[1,2-*a*]quinolino-5-carbonitrile (**4e**) grown by crystallization from ethanol were as follows: *a* 10.3827(12), *b* 12.1714(18), *c* 14.8154(14) Å; *V* 1872.3(4) Å^3, d_{calc} = 1.222 g/cm^3. Space group $P2_12_12_1$, *Z* 4. Crystal dimensions: 0.47×0.43×0.35 mm.

A total of 1422 reflections with $I > 2\sigma(I)$ were measured. The structure was solved by the direct method using the SHELXTL-97 software package [16]. The positions and temperature parameters of the non-hydrogen atoms were refined isotropically and then anisotropically by the full-matrix method of least squares to R_1 0.0751 and wR_2 0.0519. The hydrogen atoms were localized using electron density maxima and refined using the "rider" model. The complete crystallographic data were deposited at the Cambridge Crystallographic Data Center (CCDC deposit 924906).

Kinetic Experiments. The kinetic measurements of propenenitrile **3a** cyclization were performed using ^1H NMR spectroscopy on a Bruker Avance II spectrometer in DMSO-d_6. Reactant **3a** (0.02 mmol) was dissolved in DMSO-d_6 (0.5 ml). A sealed NMR tube was placed into the instrument and the spectrum was acquired. Then the tube was heated to the required temperature and spectra were acquired at given time intervals. The temperature was maintained and monitored by the instrument during the experiment. The DMSO-d_6 absorption peak was used as an internal standard signal.

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